

CONFIDENTIAL
September 26, 2017

Eric Mueller
Regulatory Officer
Kansas City District Office
10918 John Galt Blvd
Omaha, Nebraska 68137

Re: Response to FDA Warning Letter Dated September 5, 2017 Relating to Food and Drug Administration ("FDA") Form 483, Issued March 24, 2017, FEI Number 1950222

Dear Mr. Mueller,

This letter, the following response, and the accompanying attachments respond to the FDA's Warning Letter, dated September 5, 2017 ("Warning Letter"), that was issued to Meridian Medical Technologies, Inc. (hereafter "MMT") and relating to FDA's February 20 – March 24, 2017 inspection at our facilities in St. Louis, Missouri.

We appreciate the input provided by the seven investigators who conducted the MMT inspection. This several week inspection was supported by a national expert on medical devices and a national expert on aseptic processing, and was the first time the site underwent an inspection that focused on combination product current Good Manufacturing Practice ("cGMP"). This mix of expertise and expanded focus, we believe, resulted in constructive feedback for the site. We take FDA's concerns seriously, and we believe our responses demonstrate a thorough assessment of each of the Warning Letter issues, and corresponding commitments to address the concerns.

Significance of EpiPen and Potential Product Quality Concerns

EpiPen® and EpiPen Jr® (epinephrine injection) Auto-Injectors (collectively "EpiPen") are drug-device combination products indicated for the emergency treatment of sudden life-threatening allergic reactions to insect stings or bites, foods, drugs, or exercise. The anticipated users of EpiPen are non-healthcare practitioners; specifically, patients and patient caregivers in an emergency. MMT recognizes the critical role that this product plays in the lives of patients, and the reliance that patients, caregivers and medical practitioners place on the functionality of the epinephrine injection device in an emergency. For this reason, MMT would like to offer some additional information on patient safety to help address issues raised by FDA in the Warning Letter.

The Warning Letter states, among other things, that MMT "failed to thoroughly investigate multiple serious component and product failures for your EpiPen products, including failures associated with patient deaths and severe illness," and that MMT "received hundreds of complaints that your EpiPen products failed to operate during life-threatening emergencies, including some situations in which patients subsequently died." At the outset, MMT would like

to clarify that based on the company's comprehensive review and assessment of relevant data in its adverse event database from September 8, 2015 to September 7, 2017, no evidence has been found of a causal link between patient deaths and reports of failure of EpiPen units to activate. Moreover, MMT reviewed the results of its release testing, retain sample testing and complaint sample evaluations and has only identified 1 confirmed process related complaint for a failure to activate and 1 confirmed process related complaint for difficult to activate. Both units were from a single lot (5FA665), which was among the 22 lots of EpiPen recalled by the company earlier this year. On the basis of our review, we are confident in the quality and performance of our product on the market. Subsequent to the issuance of the Warning Letter, FDA confirmed in an announcement on its website that it is not aware of defective EpiPens currently on the market.

While the review of complaint data from the past 2 years demonstrates 1 confirmed failure to activate complaint and 1 confirmed difficult to activate complaint out of more than (b) (4) units shipped (MMT recognizes that it does not have established usage data), MMT agrees that opportunities exist to improve its investigation process, its broader Quality Systems, and the product. MMT is working diligently to implement corrective actions, controls, and oversight that will bolster its Quality Systems. The attached response details actions taken at the site to date, and comprehensive actions that MMT is taking to further improve its operations and ensure ongoing compliance with cGMP.

Management Commitment and Engagement

Our senior management team understands the issues and concerns that led to the issuance of the Warning Letter and fully appreciates the need for a comprehensive response and strong corrective and preventive actions ("CAPAs") to address these issues and concerns. Your Warning Letter has received the attention of senior members of Pfizer management, and management is committing the necessary financial and personnel resources to comprehensively address FDA's inspectional observations and ensure sustainable compliance with the requirements of cGMP and Quality System Regulation ("QSR"). As previously committed in our 483 response and update, MMT is completing a comprehensive review of its Quality System and, where needed, leveraging external expertise and resources. Senior management will ensure these commitments, outlined here and previously in our 483 response and update, are implemented accordingly.

Compliance Action Plan

On July 30, 2017, in our first update to the FDA Form 483 response, we provided a Compliance Action Plan ("CAP") that addressed both the specific inspection observations from FDA and served as an opportunity to assess our Quality System more comprehensively. The CAP covered several subsystems, including design controls, complaint management, and CAPAs, secured management input and oversight, and outlined a specific timeline for completion of commitments. MMT also retained a third-party cGMP consultant to audit specific subsystems that were implicated in FDA's inspection and/or warranted attention based on the site's own review. MMT, in collaboration with the third-party cGMP consultant, then developed a CAPA plan to address observations made during those audits. CAPA continue to be added to the plan

as the third party system assessments are completed, evaluated, and responded to by MMT (with above site engagement in this process).

MMT has made significant progress in completing its CAP, and will continue to address the actions in accord with its timeline. The CAP is a critical component to enhance MMT's Quality System following FDA's inspection, and the company will leverage its CAP commitments to further address FDA's concerns identified in the Warning Letter. MMT views the CAP and this response as complementary to one another, with the ultimate goal of evaluating and enhancing its overall Quality System.

Additional Commitments Beyond the CAP

Beyond the CAP, and in light of FDA's concerns from the Warning Letter, MMT has developed a systematic course of actions to further enhance its Quality System. MMT understands how these issues, as noted by FDA, could potentially impact product quality and safety if left unaddressed. While MMT's commitments are detailed in its enclosed response, we provide a brief overview of the significant actions the company is taking.

Improving Quality of Investigations

MMT understands the criticality of thorough and accurate investigations to identify and promptly address any potential product issues. While MMT believes its investigations confirm there is a low risk of its EpiPen products failing to activate, the company also recognizes that there are opportunities to improve its investigation process overall, as observed by FDA.

As noted above, MMT has begun implementing actions to enhance its investigations through its CAP. Prior to receipt of the Warning Letter, a third-party cGMP consultant audited MMT's investigation process, and MMT collaborated with that expert to develop specific CAPAs addressing the findings from that audit, including updating and clarifying investigation-related procedures and aligning to patient risk, enhancing the trending process, and improving traceability to the elements of product design.

MMT also appreciates the importance of a sound training program to ensure investigations are well-developed, incorporate critical analysis, and identify root causes. To that end, the company is enhancing the existing training program, with an emphasis on combination products and device requirements. In addition, MMT is committing to contract a third-party cGMP consultant to conduct batch record reviews of EpiPen, which will include a review of any associated nonconformance investigations, while the site bolsters its overall Quality System.

Aside from improving the investigation process, MMT is conducting a comprehensive review of its manufacturing investigations, as requested by FDA. The company, with corporate personnel and external subject matter experts, developed a protocol to conduct this review, focusing on quality-related reports (internally known as QARs) opened and approved from September 8, 2015 through September 7, 2017. MMT has executed that protocol and is following up on its observations, which are discussed in more detail below.

Complaint Handling and Response

Complaint prioritization classification was revised on September 26, 2017 to ensure that the prioritization was based on the potential harm to the patient (patient risk). The new prioritization was determined by a risk assessment, based on a Hazard Analysis List (“HAL”) and design Failure Modes Effects Analysis (“dFMEA”). A retrospective review of complaints categorized and prioritized under the prior definitions is underway to ensure that the historical complaints were investigated appropriately.

Moreover, in conjunction with its marketing partner Mylan, MMT will collaborate to identify additional potential opportunities to strengthen MMT’s joint quality and safety review of the quality and pharmacovigilance data, and will update its Quality Agreement to further align with QSR requirements.

Fulfilling Transition to QSR Compliance

Historically, MMT has manufactured EpiPen in accord with drug cGMP, and has relied on its Quality System focused on those specific requirements to ensure product quality, safety, and efficacy. MMT has complete confidence in that aspect of its Quality System, and recognizes that additional measures should be taken given the combination product status of EpiPen and other products manufactured at the MMT sites.

As the regulatory framework for cGMP for combination product has evolved through rulemaking and guidance, FDA’s expectations for compliance have become clearer. MMT understands it needs to continue to build out its Quality System to meet these compliance concerns with respect to QSR. Thus, MMT is accelerating its expansion of its Quality System to encompass specific QSR requirements for combination products, for example, design controls.

Specifically, MMT is implementing a methodical approach to apply design controls and other requirements under 21 C.F.R. § 820.30 to currently marketed products, products subject to premarket review, and new products intended to be marketed in the future. Greater focus will be placed on ensuring documentation clearly demonstrates that product meets user needs and intended use on a consistent basis. Moreover, MMT will re-evaluate its product design process, for both current and future products, to ensure appropriate design verification and design validation procedures are conducted.

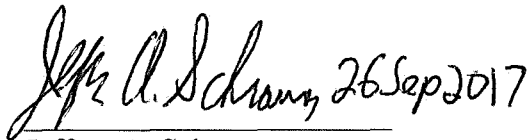
MMT is committed to enhanced integration of various device QSR requirements in accord with FDA’s streamlined combination product regulation and guidance into its existing Quality System. MMT also commits to conduct a comprehensive QSR gap assessment with oversight and input from a third party cGMP consultant.

Conclusion

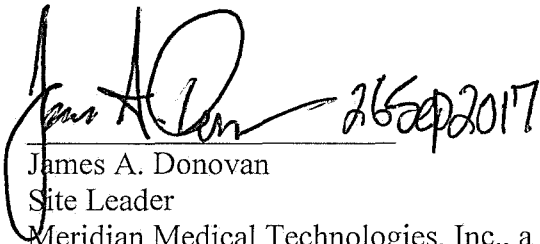
MMT will continue to work diligently to address FDA’s concerns. The company also looks forward to meeting with FDA at a regulatory meeting in the near future. MMT will include updates on the status of our commitments in the quarterly CAP updates as previously outlined to the Agency; the next of which will be submitted by October 31, 2017.

If you have any questions about our response or wish to provide input, please do not hesitate to contact us.

Sincerely,



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Enclosure(s): [Response to Warning Letter and accompanying attachments]

Cc:

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**MERIDIAN MEDICAL TECHNOLOGIES' RESPONSE TO FDA'S SEPTEMBER 5, 2017 WARNING
LETTER**

Submitted September 26, 2017

EXECUTIVE SUMMARY

Introduction

In its September 5, 2017 Warning Letter (“Warning Letter”), FDA noted seven specific concerns with MMT’s manufacturing operations and Quality System. For ease of reading, MMT has organized the Warning Letter response into seven sections; each section contains MMT’s response to FDA’s concerns, and describes commitments made in response.

MMT understands FDA’s concerns and is committed to addressing each of them in a holistic and conclusive manner. To that end, MMT commits to numerous actions in the response below, each designed to address FDA’s concerns, improve operations at the site, and better align with combination product current Good Manufacturing Practice (“cGMP”) requirements.

MMT is committed to ensuring the quality of the EpiPen and EpiPen Jr (epinephrine injection USP) Auto-Injectors (“EpiPen”), and that it is meeting cGMP requirements for combination products, including specific provisions under the Quality System Regulation (“QSR”) for its device constituent parts. To provide an additional level of quality oversight and feedback to the site, MMT is committing to contract a third-party cGMP consultant to conduct batch record review for EpiPen batches, which will include a review of relevant investigations. Also, as committed in MMT’s April 14, 2017 Response to FDA 483 dated March 24, 2017 (“483 response”), with further details summarized in the Compliance Action Plan (“CAP”) submitted to FDA on July 30, 2017, MMT will have a third-party cGMP consultant conduct effectiveness checks on the corrective and preventive actions (“CAPAs”) implemented as a result of the CAP.

Drug cGMP Regulations

In response to Drug cGMP Regulations section 1 of the Warning Letter, MMT addresses FDA’s concern with the adequacy of investigations into reports that EpiPen units failed to activate when needed by a user. In this section MMT notes that no evidence has been found of a causal link between patient deaths and reports of failure of EpiPen units to activate. MMT explains the investigational activities conducted with respect to failure to activate complaints, outlines the relevant complaint and pharmacovigilance data and decisions to recall, and notes actions taken and commits to further enhance Quality Systems and investigations. MMT summarizes the status of its comprehensive assessments of manufacturing investigations, which is supportive of the quality of product on the market and concludes no market action is required.

In response to Drug cGMP Regulations section 2, in the subsection titled “Complaint Classifications” of the Warning Letter, MMT responds to FDA’s concern that the rationale for determining complaint prioritization was not provided to the Agency and that MMT did not describe its plan for reviewing complaint prioritization under the previous plan. In response, MMT explains its current rationale for complaint prioritization that was revised on September 26, 2017, which aligns with potential patient risk, and describes a plan to assess complaints received prior to implementing the revised prioritization scheme. In the subsection titled “Trend Analysis”, MMT responds to FDA’s concerns that complaint trending at MMT does not evaluate trends across lots. In this response, MMT also provides details on how trending complaints between lots will be accomplished, and summarizes an analysis of complaint trends for all lots distributed within the last two years.

Device QSR Requirements

In the Preamble to MMT's response to FDA's concerns related to QSR, MMT provides an overview of device controls in place at the site, MMT's belief that systems and processes ensure the quality of product manufactured at the site, and a commitment to conduct a comprehensive QSR gap assessment for combination products with oversight and input from a third-party cGMP consultant.

In Device QSR Requirements section 1, subsection "Causes of Nonconformities" of the Warning Letter response, MMT addresses FDA's concern with the site's identification and assessment of the causes of failure modes of components and (b) (4). In response, MMT describes its procedure for assessing the level of units (b) (4), and how this information feeds into analysis of processes and the CAPA system. In the subsection titled "Process Capability Analysis", MMT addresses FDA's concern with the statistical methodology used to analyze process capability at critical steps to detect recurring problems and facilitate accelerated continuous improvement. In response, MMT outlines the approach to be taken for process capability studies conducted at the site, and how the information will be used to improve processes and identify CAPAs. In the subsection titled "Statistical Methodology and CAPA", MMT addresses FDA's concern regarding analysis of complaint trends. In response, MMT describes its process for trending complaint data, including for issues not associated with a lot, and how complaint trends will be addressed with CAPAs.

In Device QSR Requirements section 2 of the Warning Letter response, MMT addresses FDA's concern regarding the site's use of Acceptable Quality Limits ("AQLs") for design verification. In response, MMT indicates it will not use AQL sampling as a basis for acceptance criteria, and will instead base acceptance of design verification of essential to function characteristics on demonstrating they meet system level reliability ("SLR"). MMT also explains how it establishes the Unacceptable Quality Level ("UQL") in design verification, and demonstrates that its sampling plans are based on valid statistical methods.

In Device QSR Requirements section 3, subsection "User Needs and Intended Uses" of the Warning Letter response, MMT addresses FDA's concern with performance of design validation. In response, MMT outlines its commitment to conduct design validation, to include user studies, updated risk analysis, and submission of a design validation report. In the subsection titled "Risk Analysis", MMT responds to FDA's accurate assertion that the site did not submit its updated risk assessment for EpiPen design verification and validation to FDA by summarizing and attaching the risk assessment.

Additional Items

In response to the section of the Warning Letter titled "Quality Agreements", MMT addresses FDA's position that MMT is ultimately responsible for the quality of combination products manufactured at the site, notwithstanding a quality agreement with Mylan Specialty, L.P. ("Mylan"). In this response, MMT acknowledges its responsibilities as manufacturer, which are demonstrated in its quality agreement, and commits to update its quality agreement to capture additional 21 C.F.R. Part 4 and Part 820 requirements and responsibilities.

Finally, in response to the section titled “Repeat Violations at Facility” of the Warning Letter, the site addresses FDA’s concern that MMT was cited for similar observations in the October to November 2014 FDA inspection. MMT responds to FDA’s concerns and reassures FDA that MMT is committed to ensure sustainable cGMP compliance, including the implementation of robust effectiveness checks.

Management Commitment

To further drive sustained GMP performance, Pfizer formed a Quality Excellence Team (“QET”) with focused, dedicated leadership and resources to provide quality support and program oversight of remediation activities. The team is co-led by Operations and Quality with dual reporting to a Vice President of Pharmaceutical Manufacturing Operations and a Vice President of Quality Operations, and is sponsored by members of Pfizer’s Executive Leadership Team. The objective of the QET is to deliver a focused and aligned approach to development and execution of quality improvement activities at selected sites (including MMT) to maintain sustainable compliance at all levels of the organization.

DRUG CGMP REGULATIONS

- 1. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).**

Introduction

The first section of the Warning Letter relates to MMT’s investigation into customer reports of EpiPen failure to activate (“FTA”), EpiPen units were difficult to activate (“DTA”). In the section below (pages 6-15), MMT discusses in detail the investigation of EpiPen FTA and DTA complaints, the root cause identified, CAPAs, and market action taken on 22 lots. MMT also outlines its comprehensive review of all manufacturing investigations and plans with respect to product on the market.

EpiPen is a drug-device combination product indicated for the emergency treatment of sudden life-threatening allergic reactions to insect stings or bites, foods, drugs, or exercise. The anticipated user of EpiPen is non-healthcare practitioners; specifically, patients and patient caregivers in an emergency. MMT recognizes the critical role that this product plays in the lives of patients, and the reliance that patients, caregivers and medical practitioners place on the functionality of the epinephrine injection device in an emergency. For this reason, MMT would like to offer some additional information on patient safety to help address issues raised by FDA in the Warning Letter.

The Warning Letter states, among other things, that MMT “failed to thoroughly investigate multiple serious component and product failures for your EpiPen products, including failures associated with patient deaths and severe illness,” and that MMT “received hundreds of complaints that your EpiPen products failed to operate during life-threatening emergencies, including some situations in which patients subsequently died.” At the outset, MMT would like

to clarify that based on the company's comprehensive review and assessment of relevant data in its adverse event database from September 8, 2015 to September 7, 2017, no evidence has been found of a causal link between patient deaths and reports of failure of EpiPen units to activate. Moreover, MMT reviewed the results of its release testing, retain sample testing and complaint sample evaluations and has only identified 1 confirmed complaint for FTA and 1 confirmed complaint for DTA. Both units were from a single lot (5FA665), which was among the 22 lots of EpiPen recalled by the company earlier this year. On the basis of our review, we are confident in the quality and performance of our product on the market. Subsequent to the issuance of the Warning Letter, FDA confirmed in an announcement on its website that it is not aware of defective EpiPen currently on the market, which is aligned with MMT's conclusion.

MMT recognizes the significance of the issues cited in the Warning Letter and the potential safety impact of an auto-injector that fails to activate. MMT is committed to working with FDA to ensure that the issues cited in the Warning Letter are addressed completely. In doing so, MMT will continue to engage with the Agency in an objective review of the data and the company's plans to address the issues.

While the review of complaint data from the past 2 years demonstrates 1 confirmed FTA complaint and 1 confirmed DTA complaint out of more than (b) (4) units shipped (MMT recognizes that it does not have established usage data), MMT agrees that opportunities exist to improve its investigation process, its broader Quality Systems, and the product. MMT is working diligently to implement corrective actions, controls, and oversight that will bolster its Quality Systems. The responses below detail comprehensive actions that MMT is taking to further improve its operations and ensure ongoing compliance with cGMP.

In summary, MMT is engaged in a comprehensive plan to enhance its Quality Systems. For example, MMT developed a CAP, in collaboration with a third-party cGMP consultant, to identify CAPAs beyond those described in MMT's 483 response. The CAP, which was submitted to FDA on July 30, 2017, is designed to further enhance systems and processes in a holistic and proactive manner, and focuses on the following:

- Design controls – As described in MMT's 483 response, the site committed to update procedures governing design controls, including design inputs, design outputs, design verification, and design validation. As discussed below in response to Device QSR Requirements, section 3, in the subsection titled "Risk Analysis", the site updated the risk assessment associated with EpiPen products. A third-party cGMP consultant was also retained to help in the evaluation of design control practices and enhancements, design transfer, design verification, and design validation practices.
- Complaint Investigations – To supplement the enhancements made in its 483 response, the CAP included an audit of complaint investigations and trending practices by MMT's third-party cGMP consultant; and
- AQLs – Following the 2017 inspection MMT committed to (b) (4) its AQLs from (b) (4) to (b) (4) for critical defects, and update relevant defect classifications.

The CAP also outlined a plan for CAPA effectiveness checks, which will be completed via audit by a third-party cGMP consultant at least (b) (4) after CAPAs have been implemented. MMT also plans to implement the following improvements:

- Conduct comprehensive user studies for the EpiPen platform to ensure safe and effective use
- Conduct usability engineering studies for the EpiPen platform to minimize use-related hazards and risks and then confirm users can use the device safely and effectively
- Increase the SLR beyond (b) (4)%
- Implement a (b) (4) UQL for design qualification

MMT commits to additional improvements as discussed in response to Device QSR Requirements on pages 22-35 below.

MMT is fully committed to ensuring the quality of product. In light of the changes implemented since the March 2017 inspection and the concerns expressed in the Warning Letter, MMT recognizes that an additional level of quality oversight would be valuable to demonstrate its commitments. MMT commits to contract a third-party cGMP consultant to conduct batch record review for EpiPen batches, which will include a review of associated investigations, for at least the (b) (4), starting in November 2017. At that time, MMT will assess the need for continuing this additional level of quality oversight. MMT also recognizes the need for a sound training program to ensure investigations are well-developed, incorporate critical analyses, identify root cause, examines the impact on patient safety and, as necessary, extend to other batches and products. To that end, the company is improving its investigations training program with an emphasis on combination products and device constituent parts. With input from a third-party cGMP consultant, this will ensure MMT's investigators and relevant personnel have sufficient support to improve their product knowledge and investigations and apply appropriate investigative concepts common to a QSR CAPA program. Finally, as committed in the CAP submitted to FDA on July 30, 2017, MMT will have a third-party cGMP consultant conduct effectiveness checks of CAPAs implemented as a result of the CAP.

As demonstrated by the CAPAs implemented at the site, and the quality oversight provided by the QET and third-party cGMP consultants, MMT remains committed to addressing all of FDA's concerns, including those with EpiPen complaint investigations, in a comprehensive manner to achieve a sustainable state of compliance.

EpiPen Device Functionality

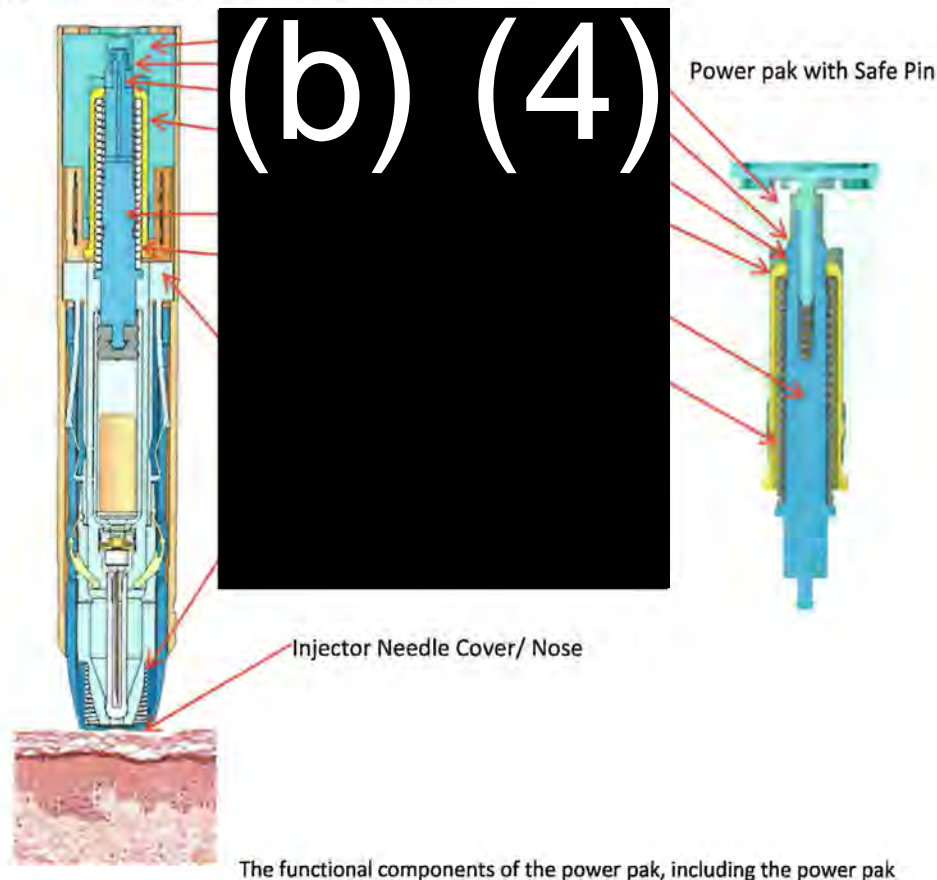
EpiPen is a single-use spring loaded hand-activated auto-injector that delivers a 0.3 ml dose of epinephrine solution to the patient upon activation. The device has a locking needle cover that post-activation/injection, will deploy, lock, and fully cover the needle from view. The auto-injector is activated when the administrator removes the safety release to ready the auto-injector, and pushes the auto-injector against the patient's thigh. According to product specification, activation should require a force of (b) (4) to (b) (4) pounds applied to the orange tip of the injector, which is transferred through the plastic cartridge container to the auto-injector's Power Pak.

The EpiPen auto-injector Power Pak is comprised of (b) (4) components which consist of: (b) (4)
At time of need, the safety

release is removed to prepare the auto-injector, (b) (4)

See Figure 1.

Figure 1 Auto-Injector with Safe Pin Removed



Investigations Related to the Power Pak Component Defect

On February 1, 2016, MMT initiated a laboratory investigation into a Power Pak failure when Power Pak lot (b) (4) (Vendor Lot (b) (4)) was received at incoming inspection and failed to meet the specification for activation force. MMT tested (b) (4) units at incoming inspection and found that 1 unit required greater than (b) (4) pounds of applied force to activate. A Laboratory Investigation Report ("LIR") was initiated on February 1, 2016, following SOP-QLA-MQA-00001, *Laboratory Investigations*, and a Supplier Corrective Action Report ("SCAR") was sent to the vendor (b) (4) on February 8, 2016, per SOP-QLC-QLE-00008, *Supplier Corrective Action Request*. At the time, the confirmed out of specification ("OOS") for an incoming component test result did not clearly require initiation of a Quality Assurance Report ("QAR") or a notification to management Quality Notification Report ("QNR"), and neither were initiated in this case.

Based on the OOS result, MMT returned Power Pak lot (b) (4) to (b) (4) and requested a root cause evaluation. The vendor's initial response to the SCAR was received on February 11, 2016, and it concluded that a temporary (b) (4) likely caused a deformed (b) (4) within the (b) (4), thus requiring increased force to activate the unit (this probable root cause was subsequently confirmed by the vendor as a reproducible failure mode in engineering studies). The vendor investigation concluded that the defect was likely isolated to one tote of finished subassemblies, based on routine in-process quality control ("QC") inspections and release testing, neither of which contained any such defects. The vendor also noted that the (b) (4) lot that was used with Vendor Lot (b) (4) was also used with lot (b) (4), though the sister lot was likely not impacted by the defect due to the isolated nature of (b) (4) that would have caused the deformed (b) (4). As a precautionary measure, though, MMT also rejected lot (b) (4) on September 8, 2016. The vendor conducted an evaluation of all the returned Power Pak units from lot (b) (4) ((b) (4) units reviewed) and determined that (b) (4) additional units had flashing in the (b) (4) area, which - even though all sub-assemblies did activate - might have necessitated increased force to activate. In its report, the vendor noted that there was no evidence in its complaint data of a Power Pak FTA within the past 5 years, during which time (b) (4) Power Paks had been manufactured.

On May 9, 2016, MMT evaluated an EpiPen complaint sample (one unit from Lot 5FA665) the site had received for a complaint from a patient involving a unit which was reported as a FTA. As part of the complaint investigation, the sample was disassembled and the (b) (4) within the (b) (4) was observed to be deformed. The deformation of the (b) (4) prevented the unit from activating. An investigation in the (b) (4) ((b) (4)) (PR22268) was initiated, as well as a Field Alert Report ("FAR"). As part of the investigation, a SCAR was issued to the Power Pak vendor to initiate an investigation into the root cause of the defective (b) (4). The report from the vendor indicated that they inspected the (b) (4) of over (b) (4) across multiple lots and found no other defective (b) (4). MMT reviewed the complaint data, and, with one confirmed FTA complaint from a deformed (b) (4) and over (b) (4) units examined, closed the FAR and indicated that no market action would be initiated.

In July 2016, during a final review of (b) (4) records to close out the investigation for the failed incoming inspection, MMT noted that the vendor associated an additional Power Pak (b) (4) lot with the manufacturing of the rejected Power Pak lot from February 1, 2016. A lot trace was conducted and it was determined that this additional (b) (4) lot had been used in the manufacture of (b) (4) additional Power Pak lots, which were used in (b) (4) distributed lots. Working with (b) (4), MMT identified a number of Quality System gaps and corrective actions that would prevent a repeat event. In October 2016, this investigation was closed with no additional confirmed failures to activate.

On December 20, 2016, a DTA complaint was received on Lot 5FA665, the same lot from the previous FTA complaint. Based on the event narrative which described difficulty in activating the device before successful activation, MMT initiated a FAR (December 23, 2016). The complaint sample was returned to MMT, and was inspected and disassembled on January 17, 2017. While the unit had been activated prior to being returned, the (b) (4) was found to be deformed. Based on the findings of the investigation, including the number of confirmed complaints classified as FTA (1) and the number of low level of defects identified across

significant component reviews, MMT closed the FAR on February 16, 2017, and communicated that it would not initiate market action.

During the course of the 2017 FDA inspection, MMT re-opened the FTA complaint investigation, and on March 9, 2017, the issue of (b) (4) defects was brought to a cross-functional quality review team meeting to consider a recommendation to initiate market action. Statistical analysis included as part of the presentation to the team indicated that while lot 5FA665 had only one confirmed complaint for FTA and one confirmed complaint for DTA, the total number of complaints of this nature were close to a statically higher level than the historical norm for other Lot 5FA665 had a complaint rate of (b) (4)% when compared to the historical value of (b) (4)% per lot (the lot complaint rate was also higher than the 21 lots that were subsequently recalled). Therefore the recommendation to the quality review team was to recall Lot 5FA665. Following additional discussions with FDA on March 27, 2017, MMT decided to recall all 22 finished good lots potentially associated, through sub-assembly and component lot genealogy, with a deformed (b) (4). At the time of the initial recall these lots were not within the scope of the recall because there were no confirmed complaints for “Failure/Difficult to Activate” and the overall complaint rates for these lots (b) (4)% were at or below the historical norm of (b) (4)% per lot.

Since the FDA inspection, as referenced in MMT’s 483 response (response to Observation 1A), the site has updated SOP-QLA-MQA-00004, *Notification to Management* to require a Quality Notification Report (“QNR”) for any incoming component testing failure. Issuing the QNR will assure that the full lot trace from the vendor occurs within (b) (4), and the need to submit a FAR can be timely evaluated. In addition, the site has updated the SCAR procedure (SOP-QLC-QLE-00008, *Supplier Corrective Action Request*) so that all SCARs, involving any GMP materials or components, will require the initiation of a QAR. Completion of a QAR will further assure that a quality impact assessment occurs within (b) (4) of discovery of a quality concern.

MMT is currently in the process of establishing an updated Quality Agreement with the Power Pak vendor to enhance its purchasing controls. MMT has identified the following items that would improve the current Quality Agreement, and will negotiate with the vendor in an effort to include these items in the Agreement: (b) (4)

MMT is also implementing improvements to its change management processes. For example, the Site Change Management procedure was enhanced to incorporate a formalized risk management assessment of patient impact due to post-market design changes. This change in procedure requires all site changes to be assessed for potential impact to the device with respect to patient use. If the initial assessment concludes that there is potential impact to the device, an in-depth impact risk assessment of the change with respect to the design verification, design validation, and design history files will be conducted. Based on this assessment, a Design Change Action Plan is created to assure that the change will not impact the use of the device by the patient and that the design history files are updated. The Site Change Management process also requires a risk analysis document and a change effectiveness check for all major changes. This process is reflected in attached SOP-QLA-GEN-00802, *Site Change Management Process*, with associated templates, TMP-DSG-DEV-CHG-01, *Design Change Decision*, TMP-DSG-DEV-CHG-02, *Design Change Impact Assessment*, TMP-DSG-DEV-CHG-03, *Design Change Action Plan*, and TMP-DSG-DEV-CHG-04, *Design Change Project Closure Review* (Attachment 1).”

All CAPAs noted in MMT's 483 response to prevent (b) (4) defects from occurring have been implemented at the supplier. MMT has also completed all CAPAs associated with this investigation, many of which increase the controls for Power Pak performance, lowering the overall risk to patients. Since these controls have been implemented, no defective (b) (4) have been detected by our supplier or during our incoming inspection process.

Both the manufacturing and complaint investigation processes are being updated to closely interlink the two investigation processes. Manufacturing investigations will be formally evaluated for their potential to impact patient use and safety as well as product quality. If the initial assessment concludes that there is potential impact to the device or device constituents, an SME will be required to review the investigation to ensure the investigation examines the deviation's impact to the batch as well as the impact to other batches. In the complaint investigation procedure, a formal risk assessment will be completed to assure that all potential patient hazards are considered as part of the root cause analysis and identified corrective actions. These procedures, SOP-QLC-QLE-00702, *Product Complaint Handling* and SOP-QLA-MQA-00720, *Event and Deviation Reporting (ER&QAR)* will be updated by November 30, 2017.

Finally, MMT has created a new leadership role within the quality organization, Combination Product Program Director, to oversee three critical systems in managing ongoing device performance including; Design Control, Risk Assessment Management and Life Cycle Management. This will include integration of the streamlined QSR requirements, such as CAPAs, design controls and purchasing controls.

Complaint Investigations and Complaint Sample Disassembly

Upon receipt of a complaint by a complaint intake center, representatives request return of the complaint sample. Historically, disassembly of complaint samples was dependent on the complaint type, the state of the sample returned, and the information within the complaint narrative. In November 2016, MMT implemented JA-DVL-PDV-10803, *Complaint Sample Evaluation Job Aid* (Attachment 2), which detailed the laboratory evaluation steps to be performed for complaint samples, depending on complaint subclass and returned sample condition. This initial version of the procedure contained non-invasive and non-destructive minor disassembly instructions (such as removal of the label to allow the basic unit to be inspected thoroughly and removal and inspection of the safe pin for spontaneous activation complaints), which did not require management approval. The procedure also referred to obtaining Site Quality Operations Leader ("SQOL") approval for any significant disassembly, such as any investigations that would require cutting into the device.

As discussed during the 2017 inspection, significant disassembly of returned units poses potential safety risks and is a destructive operation. MMT established a requirement for SQOL approval of disassembly request for the following reasons:

- Returned units have been outside of MMT's control and are returned in an unknown state;
- Units are highly energized due to the (b) (4) within;
- Biohazards may be present on returned units used on patients;
- Disassembly is a destructive operation that may result in loss of evidence for a quality investigation; and

- Disassembly requires use of machinery that poses risks to colleagues (e.g. laceration).

Following the first confirmed complaint for Lot 5FA665, which was confirmed on May 9, 2016, MMT enhanced its scrutiny of the complainant's description of the reported issue for FTA complaints. As a result, complaint samples (and the Power Pak components) were disassembled if the complaint narrative indicated difficulty in activating the unit, regardless of whether the unit was returned in an activated state. It was under this process that the deformed (b) (4) was discovered in the December 20, 2016 complaint for Lot 5FA665 reporting DTA, as the complaint sample was later returned to MMT in an already activated state and was disassembled to evaluate the Power Pak components.

MMT updated procedure JA-DVL-PDV-10803, *Complaint Sample Evaluation Job Aid* on February 28, 2017¹ (Attachment 3) to require disassembly of units and Power Paks of (b) (4) for FTA/DTA complaints regardless of the received state of the injector or complaint narrative. Furthermore, the procedure was updated to require functional testing (b) (4) be performed prior to disassembly on all un-activated injectors for complaints of this nature. This change was made so that functional test performance against registered specifications could be verified prior to any disassembly. Under this enhanced process, no returned complaint samples tested to date have failed functionality specifications.

On March 15, 2017, MMT submitted a follow-up FAR regarding the investigation of complaints received for Lot 5FA665. In the FAR, MMT stated that, between January 1, 2014 and March 15, 2017, the site received 171 complaint samples associated with reports of "Proper Sequence Followed but Injection/Activation Failed" and of the 171 samples received, (b) (4) were disassembled. Following receipt of the Warning Letter, MMT conducted a comprehensive analysis under protocol of the rationale for not disassembling complaint samples (for "Proper Sequence Followed but Injection/Activation Failed"). In conducting this evaluation, MMT determined that it had received 210 complaint samples in the above time period for this complaint subclass and (b) (4) of them were disassembled to evaluate the Power Pak components. There were 180 individual complaint records received for this subclass over the given time period which had one or more associated samples returned. Of the 180 complaint records, (b) (4) had the directly associated sample disassembled to evaluate the Power Pak components. Many of the samples did not have a direct association with the complaint, but were submitted by the complainant along with the subject sample and where laboratory evaluated in addition to the direct subject sample.

It was also confirmed that for instances (associated with this subclass) where the site received the complaint sample after April 1, 2016, the Power Pak was disassembled and the (b) (4) evaluated in (b) (4) samples returned by the complainant. The only confirmed failures for DTA/FTA remain the single FTA for Lot 5FA665 and the single DTA for Lot 5FA665 (the lot has been recalled). Below is a summary of the 135 complaint reports in this subclass with

¹ During a commitment review, it was determined that the revisions to procedure JA-DVL-PDV-10803 were incomplete. The procedure was promptly updated to completely align with the 483 commitment and the (b) (4) units that, pursuant to the incompletely revised SOP had only been examined in a laboratory to a point that confirmed no product quality issue existed and had not been disassembled, were disassembled. The additional (b) (4) disassembled units all supported the investigation's original conclusions.

returned samples where the direct subject sample associated with the complaint did not have the Power Pak disassembled, and the associated rationale for why disassembly of the Power Pak did not occur, in line with then-current procedure:

- (b) (4) of the 135 complaints had the associated complaint sample received by MMT in an un-activated state. These were all successfully activated in the complaint sample testing laboratory. Because the samples activated, they were not disassembled.
- 107 of the 135 complaints had the associated complaint sample received by MMT in an already successfully activated state.
 - 48 of the 107 complaints were for DTA/FTA, and the samples were received in an activated state, although the complaint narratives indicated the unit had not activated according to patient perception at time of use. These complaints were considered “non-confirmed” as device functionality-related complaints, because they had, in fact, activated.
 - For 57 of 107 samples, the complaint narrative indicated that the patient interpreted themselves that the injector did in fact activate during use, however, either; the needle did not come out, there was DTA, or a perception that a full dose was not administered:
 - 31 of the 57 stated the needle did not come out, but laboratory testing confirmed that the needle had, in fact, extended properly and was covered by the protective needle cover upon receipt of the sample.
 - In 17 of the 57 complaint narratives, the user indicated that the unit was DTA (multiple attempts to successfully activate or excess pressure to successfully activate). MMT received the samples and conducted a preliminary analysis, which included visual inspection and review of the complaint narrative, and based on then-current practice determined that additional investigation was not required. As noted in this response, MMT has revised its procedures to require that (b) (4) complaint samples involving activation issues be disassembled to evaluate the Power Pak components. There have been no DTA complaints received activated after October 10, 2015 without having the Power Pak disassembled to evaluate components. There are no returned complaint samples for EpiPen lots still within shelf life of this nature that did not have the Power Pak disassembled to evaluate components.
 - In 7 of the 57 complaint narratives, the user indicated that a full dose was not delivered. Laboratory evaluation of the returned samples confirmed that the plunger moved to the expected position, for a properly delivered full dose in 6 of the 7 returns. In the 7th return, the complainant disassembled the samples so the injector function was unable to be assessed.
 - In 2 of the 57 complaint narratives, the user indicated that the needle failed to fully/properly come out of the auto injector. Laboratory evaluation concluded that the needle exited the needle cover hole as expected in both investigations. One investigation determined the needle extended as expected. The complainant stated the injector pulled away after activation during use, but a root cause was unable to be determined in the laboratory. In the 2nd complaint, the needle was bent and the laboratory hypothesized

that the needle hit a hard surface at the time of activation based on the evidence.

- 1 of the 107 complaints was for a FTA complaint, however, the complainant returned the injector in a disassembled state, therefore functionality performance was unable to be assessed.
- 1 of the 107 complaints had a complaint narrative that had minimal information and stated the “pen did not work”. Laboratory examination determined the pen activated. This was in August 2014, prior to the procedural enhancement to disassemble the Power Pak for complaints of this nature.

A follow-up FAR will be submitted to FDA noting the updated findings.

Additional enhancements were made to the complaint sample evaluation procedure JA-DVL-PDV-10803, *Complaint Sample Evaluation Job Aid*, after the 2017 inspection, which provided for enhanced colleague safety and investigational evidence product protection. For example, as noted in the April 14, 2017 revision (Attachment 4), MMT (b) (4) to (b) (4). The fixture allows for (b) (4) during the (b) (4) process, better protecting colleagues from projectile parts and biohazards. MMT has made additional procedural enhancements to JA-DVL-PDV-10803 (See version 4.0 as Attachment 5, and version 5.0 as Attachment 6) to add additional complaint subclasses that mandate disassembly based on patient risk and potential failure modes. These involve extraction of the internal components within the injector and examination. All prior complaint sample inventory that were not originally disassembled (because they were received before the procedural updates mandating disassembly) were disassembled and evaluated. There were two complaints confirmed for spontaneous activation, neither related to manufacturing or process.² MMT did not identify any defects in the remaining units, and those complaints remained unconfirmed complaints. See the next page for a table of the complaint sample data by subclass for this retrospective sample evaluation work.

The two confirmed complaints were a result of a defect not observed by the technician that originally evaluated the samples due to a lack of detail in JA-DVL-PDV-10803. This job aid will be updated to include specific detail on examining the safety release component related to this type of complaint by October 6, 2017.

A CAPA will be initiated to evaluate potential changes to the device to eliminate this use-related error. The evaluation will be completed and summarized along with a plan by November 15, 2017 regarding the testing and validation of the change.

² Spontaneous activation can occur through a use-related error under certain circumstances. The current instruction to remove the safety release is to “Remove the blue safety release by pulling straight up without bending or twisting”. If the user “peels” the safety release off by (b) (4) rather than pulling straight up, the (b) (4) and (b) (4). This can only occur if the (b) (4). This use-related action is atypical and requires a great amount of force bending the safety release to an extreme condition to cause spontaneous activation.

Complaint Subclass	Activated or Un-activated	Number Re-Evaluated	Disassembly and Lab Evaluation Results
Lack of Effect	activated	9	Units evaluated, no confirmed complaints
	un-activated	2	Units evaluated, no confirmed complaints
Spontaneous Activation	activated	82	Units evaluated, no confirmed complaints due to manufacturing or process defects. Two confirmed complaints with post-manufacture damage. (see footnote 2 on prior page for details)
	un-activated	17	Units evaluated, no confirmed complaints
Failure to Activate/ Difficult to Activate/ Multiple Attempts Required to Inject	activated	3	Units evaluated no confirmed complaints
	un-activated	3	Units evaluated, no confirmed complaints
Foreign Object/Material	activated	0	Units evaluated, no confirmed complaints
	un-activated	4	Units evaluated, no confirmed complaints
Liquid Atypical Color/Cloudy	activated	1	Units evaluated, no confirmed complaints
	un-activated	2	Units evaluated, no confirmed complaints
Container Leaking/Cracked/ Empty	activated	2	Units evaluated, no confirmed complaints
	un-activated	3	Units evaluated, no confirmed complaints
Bent Needle/Missing component/ Injector Broken-Defective/ Broken Component	activated	22	Units evaluated, no confirmed complaints
	un-activated	15	Units evaluated, no confirmed complaints

In addition to internal improvement actions undertaken by the site, MMT also retained a third-party cGMP consultant (b) (4) to evaluate specific subsystems within its Quality System. As noted in its 483 response and further elaborated in its quarterly update, MMT enlisted a third-party cGMP consultant to review selected subsystems that, based on FDA's concerns and the company's own assessment, warranted attention beyond the site's own review. Working with the third-party cGMP consultant, MMT selected these topics with the intention of identifying potential issues and areas for improvement, followed by swift and comprehensive corrective action.

The CAP specifically incorporated review by (b) (4) of MMT's Complaint Handling and Investigation System, focusing on its complaint investigations, deviation reporting and investigations, laboratory investigations, and CAPA program. Over the course of its (b) (4) audit, (b) (4) evaluated various Quality processes touching on investigations and investigation management and identified several areas of improvement. These areas included: governing procedures; training; sample logs for laboratory testing; and root-cause identification and analysis. MMT developed CAPAs in response to (b) (4) input, and included a description of the CAPAs in the CAP that was submitted to FDA on July 30, 2017. MMT has made significant progress in completion of the CAPAs.

Management at the corporate and site levels continues to oversee the progress of the CAP and related CAPAs. Moreover, MMT will retain another third-party cGMP consultant to conduct effectiveness checks of the CAPAs after a sufficient implementation period has passed.

Comprehensive Retrospective Review of all Manufacturing Investigations

In the Warning Letter, FDA requested that MMT conduct a comprehensive review of all EpiPen manufacturing investigations. In response, MMT, in conjunction with Pfizer and external subject matter experts, developed a protocol to conduct a comprehensive retrospective review of all EpiPen related QARs opened and approved between September 8, 2015 through September 7, 2017. This assessment reviewed the details of the investigations, the decision-making process, the root cause analysis, and potential impact of the deviation or event on other lots and to patient safety. The review also examined the scope and the extent of the investigation to ensure all potentially impacted lots have been considered within the manufacturing investigation, including lots of common components. The execution of the protocol, which included review of 340 deviations, is complete. Of the deviations escalated (29) for above site review, the underlying batches either underwent a comprehensive remediation plan or were rejected. The site's review has concluded that, while there were a number of QARs that needed additional review and clarification, the documented scope was appropriate in each case and patient safety was supported. A summary of the assessment can be found as Attachment 7. The details and conclusions of this comprehensive review were presented and endorsed by the above-site cross-functional Area Quality Review Team (AQRT) on September 26, 2017; MMT does not intend to take market action.

MMT will also conduct a comprehensive retrospective review of the manufacturing investigations for the site's other marketed products, pursuant to similar protocols, which will be developed and executed by November 1, 2017. A summary report of the retrospective reviews will be included in future quarterly updates to FDA.

Additionally, a comprehensive review of SCARs initiated from September 8, 2015, through September 7, 2017, which did not result in manufacturing investigations (internally known as QARs) was performed under a protocol. The protocol identified 5 of the 133 SCARs as requiring additional review to determine the potential for impact to product quality or patient safety. These 5 SCARs were then assessed using the same criteria as used for the manufacturing investigations. Of those deviations escalated for above site review, each was found to have been subject to a comprehensive remediation plan with any impacted batches having been rejected.

Finally, MMT will conduct a similar retrospective review, under protocol, of other failures or discrepancies that did not result in manufacturing investigations, such as multi-tiered specifications for incoming or finished goods. A plan for these additional reviews will be included in the next 483 quarterly update (October 31, 2017).

To further enhance the routine evaluation of patient safety and product quality complaint information reported for EpiPen, MMT is committing to enhancing the site's Management Review processes. MMT will assess additional opportunities to enrich the current process for incorporating review of relevant adverse event data in conjunction with our pharmacovigilance team. This will be incorporated into existing MMT Site Quality Review Team ("SQRT")

meetings and quality meetings that take place jointly with the pharmacovigilance team on a (b) (4) basis, starting in November 2017.

As communicated to FDA in our last 483 quarterly update on July 30, 2017, MMT is currently in the process of undergoing a third-party assessment of QSR requirements for combination products, including Management Responsibility. The CAPA outcomes of this assessment along with planned completion dates will be communicated to FDA in the next quarterly update.

Actions:

- MMT will contract a third-party cGMP consultant to conduct batch record review for EpiPen batches, which will include a review of associated investigations, for at least the (b) (4), starting in November 2017. At that time, MMT will assess the need for continuing this additional level of quality oversight.
- MMT will enhance the existing training program, with an emphasis on combination products and device requirements. The program will be developed with input from a third-party cGMP consultant.
- MMT will establish an updated Quality Agreement with the Power Pak vendor to enhance its purchasing controls. The following items that would improve the current Quality Agreement will be negotiated with the vendor in an effort to include in the Agreement: (b) (4)
- SOP-QLC-QLE-00702, *Product Complaint Handling* and SOP-QLA-MQA-00720, *Event and Deviation Reporting (ER&QAR)* will be updated by November 30, 2017 to address or include the following:
 - To closely interlink the two investigation processes.
 - Manufacturing investigations will be formally evaluated for their potential to impact the patient use and safety as well as to product quality. If the initial assessment concludes that there is potential impact to the device or device constituents, an SME will be required to review the investigation to ensure the investigation examines the deviation's impact to the batch as well as the impact to other batches.
 - A formal risk assessment will be completed as part of complaint investigations to assure that all potential patient hazards are considered as part of the root cause analysis and identified corrective actions.
- Fill a new leadership role within the quality organization, Combination Product Program Director, to oversee quality and compliance including: Design Controls, Purchasing Controls and Quality Risk Management. This role has been posted and active recruitment is in progress.
- JA-DVL-PDV-10803 will be updated to include specific detail on examining the safety release component related to this type of complaint by October 6, 2017.
- A CAPA will be initiated to evaluate potential changes to the device to eliminate the use-related error regarding the safe pin. The evaluation will be completed and summarized along with a plan by November 15, 2017 regarding the testing and validation of the change.

- In addition to the review completed for EpiPen, MMT will conduct a comprehensive retrospective review of the manufacturing investigations for the site's other marketed products, pursuant to similar protocols, which will be developed and executed by November 1, 2017. Significant findings from the retrospective reviews will be included in future quarterly updates to FDA.
- A retrospective review will be conducted under a protocol for other failures or discrepancies that did not result in manufacturing investigations, such as multi-tiered specifications for in-coming or finished goods. A plan for these additional reviews will be included in the next 483 quarterly update (October 31, 2017).
- MMT will assess opportunities to enrich the current process for incorporating review of relevant adverse event data in conjunction with our pharmacovigilance team. This will be incorporated into existing MMT Site Quality Review Team ("SQRT") meetings and quality meetings that take place jointly with the pharmacovigilance team on a (b) (4) basis, starting in November 2017.
- As communicated to FDA in our last 483 quarterly update on July 30, 2017, MMT is currently in the process of undergoing a third-party assessment of QSR requirements for combination products, including Management Responsibility. The CAPA outcomes of this assessment along with planned completion dates will be communicated to FDA in the next quarterly update.

2. Your firm failed to establish and follow adequate written procedures describing the handling of all written and oral complaints regarding a drug product (21 CFR 211.198(a)).

Complaint Classifications

In this section of the Warning Letter, FDA outlines its view that MMT's 483 response did not provide a sufficient rationale for the prioritization of different types of complaints and did not account for patient harm. In response, MMT outlines its current rationale for complaint prioritization commensurate with potential patient risk and summarizes the site's interim plan for reviewing complaints received before the current prioritization requirements.

Before discussing how MMT revised its complaint-classification system to address FDA's concerns, it is worthwhile to discuss the preexisting system and MMT's rationales. As described in MMT's 483 response to Observation 3B, product quality complaints are initially reviewed by the Global Product Quality Complaints ("GPQC") group. Following receipt, the GPQC group assigns each complaint a class and subclass, which describe the nature of the complaint, and a priority and forwards the complaint record to the investigating site. The priority (expedited, high, or normal) determines the preliminary investigation timeline and requirement for notification to management, if applicable. The 483 response explained that expedited complaints require more rapid initial processing due to the potential need for certain specific regulatory notifications, including FARs. The GPQC group determines the priority for a complaint per GPB-QS1073, *Prioritization of Pfizer Product Quality Complaint*.

At the time of the 2017 inspection, the following complaint subclasses that apply to MMT products were expedited per GPB-QS1073, *Prioritization of Pfizer Product Quality Complaint* Version 12.0:

(b) (4)

In its 483 response, MMT committed to clarify both the GPQC group and MMT site procedures regarding the purpose for expediting complaints as described above. The response also committed to ensure that any product specific prioritization exceptions for MMT products were addressed as part of the procedure updates. As a result, the GPQC group procedure GPB-QS1073, *Prioritization of Pfizer Product Quality Complaint* was updated on June 30, 2017, (version 13.0, Attachment 8) and MMT procedure, SOP-QLC-QLE-00702, *Product Complaint Handling*, was updated on July 28, 2017 (version 17.0, Attachment 9). Following these changes, four additional subclasses that apply to MMT products were elevated to “expedited”:

(b) (4)

In addition to the information in MMT’s 483 response, the following provides additional information about the prioritization procedures in place during the inspection and currently:

- Product Quality Complaint GPQC group: While the GPQC group assigns a classification and priority to each complaint, Pfizer's Good Practice Bulletin ("GPB"), GPB-QS1073, *Prioritization of Pfizer Product Quality Complaint* explains that these are initial, best fit based on the complaint verbatim, and the class/subclass definitions. The GPB also explains that these assignments must be verified by the investigating site and that the site should reassign the classification and request the GPQC group to elevate the priority as appropriate. The GPB also states that if the investigating site has an approved risk assessment, the specific instructions in the risk assessment should be followed by the site for prioritization.
- MMT Complaints Group: MMT procedure SOP-QLC-QLE-00702, *Product Complaint Handling* requires the site to verify the initial GPQC assignments and change the classification or request an adjustment in priority as appropriate. Up until the revised procedure was approved on September 26, 2017, SOP-QLC-QLE-00702, *Product Complaint Handling* did not include or reference a risk assessment linking complaint subclass and patient risk.

Building on top of this existing framework, MMT has now assigned a classification of expedited, high or normal to each complaint subclass based on patient risk. This step-wise approach was developed across functions, incorporated historical knowledge about device functionality and complaints, and documented within the Quality System.

First, a *Hazard Analysis List, EpiPen Auto-Injector (Epinephrine)* ("HAL") (Attachment 10) was developed with input from Clinical Research and Medical Operations, Biomedical Technology, Regulatory, Product Technology, and Quality Assurance. The HAL was used to identify the patient harm/severity of harm rating for each hazard. The identified hazards allowed the complaint class/subclass to be linked to a severity of harm ranking. Second, a group of subject matter experts, including Product Technology, Biomedical Technology, and Quality, associated a hazard with each complaint class/subclass. The cross-functional group was composed of personnel with significant knowledge of auto-injector functionality and general complaint intake and handling processes. And third, a complaint prioritization (expedited, high, or normal) was assigned to each severity of harm rating, providing a link between complaint class/subclass and prioritization based on patient risk. This risk-based prioritization was documented in MTR 17-021, *EpiPen Complaint Sub-Class Prioritization by Corresponding Risk to Patient Safety* ("Complaint Prioritization Protocol") (Attachment 11). Based on the results of this protocol, all of the following subclasses that apply to MMT products will be prioritized as "expedited" going forward:

(b) (4)

(b) (4)

The following additional actions have been or will be taken to ensure that prioritization of complaints for MMT products continues to be based on patient risk under the revised classification scheme:

- MMT SOP-QLC-QLE-00702, *Product Complaint Handling* was revised on September 26 2017, (Attachment 12) to:
 - Specify priorities for the complaint subclasses that apply to MMT products based on the results of the *Complaint Prioritization Protocol* discussed above.
 - Require the MMT Complaints group to verify the initial priority assigned by the GPQC group versus the priority specified for that subclass in procedure SOP-QLC-QLE-00702 within (b) (4) of MMT receiving a complaint.
 - Require an annual review of the Complaint Prioritization Protocol by Product Technology.
 - Require the MMT Complaints group to notify Product Technology via an incident report in (b) (4) if a failure mode or complaint subclass is identified during complaints handling that is not already addressed in SOP-QLC-QLE-00702, *Product Complaint Handling*.
 - Require Product Technology to review the Complaint Prioritization Protocol to determine the need for an update in the event a failure mode or complaint subclass is identified that is not already addressed SOP-QLC-QLE-00702, *Product Complaint Handling*.
 - Require that the MMT Complaints group provide the Pfizer corporate GPQC group all future revisions of SOP-QLC-QLE-00702, *Product Complaint Handling* and the *Complaint Prioritization Protocol* following any change in prioritization of a subclass so that the GPQC group can update the GPB accordingly.

- GPB-QS1073, *Prioritization of Pfizer Product Quality Complaint* will be revised by November 6, 2017 to update EpiPen specific prioritization information in line with the Complaint Prioritization Protocol.

FDA also raised concerns about the handling of complaints received before the revised, risk-based classification system discussed above. Following the Warning Letter, MMT reviewed its prior classification process, and determined that any impact based on the prior practice does not represent a potential risk to patients. This conclusion is based on the following:

- All complaint investigations for lots distributed (b) (4) included at least the following investigation elements, regardless of the complaint priority:
 - Assessment of scope of lots impacted
 - Review of associated batch records
 - Review of records (supplier and MMT test records and inventory traceability reports) for the component lots used in the complaint lot that could be associated with the potential failure mode
 - Evaluation of recurring complaints for the lot
 - Evaluation of recurring complaint for similar products and the same subclass
 - Review of approved manufacturing and laboratory investigations for the complaint lot
 - Visual examination of product reserve samples
 - Potency testing on (b) (4) reserves samples (if available) for “Lack of Effect” complaints if there was no potency test for the lot in the (b) (4)
 - Evaluation by Product Technology of returned samples
 - Identification of root cause and CAPA.

MMT is conducting a retrospective assessment of all complaints received September 8, 2015, through September 7, 2017, that would now be classified as “expedited” instead of “high” or “normal” in order to confirm that the previous classifications did not have an impact on the completeness or outcome of the investigation. This assessment is broken down into the following parts:

- Assessment Part 1: Assess whether the complaint narrative and/or the visual examination, testing and or disassembly of returned complaint samples determined the sample function met specification with no observed defects.
- Assessment Part 2: Assess the records below for complaints that per Part 1 either have no returned sample or where Part 1 could not exclude the failure modes that could cause the reported complaint. Part 2 will include a review of the following (see Attachment 13 for the full protocol):
 - Complaint investigation
 - Complaint history of the complaint lot and associated component lots, for components that may cause the reported complaint
 - Functional and or physical laboratory investigations for same lots in the bullet above.
 - Manufacturing investigations for the complaint lot (unless already reviewed as part of the retrospective review discussed in the in Drug cGMP Regulations, section 1 of this response).

- Assessment Part 3: Develop conclusions by senior Quality operations management, including for example, the need to reopen a complaint investigation, initiate a notification to management, etc.

A summary report of the assessment will be provided to FDA in the January 31, 2018 483 quarterly status update, following the completion of the assessment.

In addition to the actions outlined above, MMT will revise SOP-QLC-QLE-00702 by November 30, 2017 to ensure that complaint investigation testing and techniques also will consider potential patient risk and escalation where appropriate. The revision will also include clarification on when a detailed investigation is not required (e.g., for an invalid lot number). This part of the procedure revision will consider for example the need to complete a detailed root cause investigation for a complaint with high patient risk even when the complaint lot is expired if the root cause potentially impacts unexpired lots.

Actions:

- GPB-QS1073, *Prioritization of Pfizer Product Quality Complaint* will be revised by November 6, 2017 to update EpiPen specific prioritization information in line with the Complaint Prioritization Protocol.
- MMT will conduct a retrospective assessment of all complaints received September 8, 2015, through September 7, 2017, that would now be classified as “expedited” instead of “high” or “normal” to confirm that the previous classifications did not have an impact on the completeness of the investigation. A summary report of the assessment will be provided to FDA in the January 31, 2018 483 quarterly status update, following the completion of the assessment.
- MMT will revise SOP-QLC-QLE-00702 by November 30, 2017 to ensure that complaint investigation testing and techniques also will consider potential patient risk and escalation where appropriate. The revision will also include clarification on when a detailed investigation is not required (e.g., for an invalid lot number). This part of the procedure revision will consider for example the need to complete a detailed root cause investigation for a complaint with high patient risk even when the complaint lot is expired if the root cause potentially impacts unexpired lots.

Trend Analysis

In this section of the Warning Letter, FDA notes that, while the commitment noted in response to Observation 3A of the 483 response stated MMT would use statistical analysis to identify potential complaint trends within a lot (“intra-lot”), it did not provide for trending of complaints between lots (“inter-lot”). The response below summarizes the current complaint trend analysis requirements, as revised, including trending between lots, and summarizes a detailed analysis of complaint trends for (b) (4).

For purposes of the discussion below, complaint “class” and “subclass” are categories that describe the nature of a quality complaint. As an example, “Injectables” is a class of complaint and “Spontaneous Activation” is one of several associated subclasses.

Current Complaint Trend Analysis Methods and Trend Analysis Commitments

As discussed during the inspection and as detailed in response to Observation 3C of the 483 response, the Pfizer corporate Global Product Quality Complaint/Data Analysis and Trending Team (“GPQC/DAT”) uses statistical methodology to analyze complaints for trends (b) (4) by product and class. The multiple statistical rules used by GPQC/DAT during this analysis are detailed in procedure QCG073, *GPQC DAT Trend Alert and Outlier Reports* (Attachment 14). Per GPQC/DAT procedure QCG060, *Complaints Data Analysis and Trending Process* (Attachment 15), trend analysis results are evaluated and any identified trends are investigated so that root cause and corrective actions can be identified. (See response to Device QSR Requirements, section 1, Statistical Methodology and CAPA, for further details on both of these GPQC/DAT procedures.) While the GPQC/DAT procedures provide both robust statistical analysis of complaint trends at the class level and investigation into the cause of class trends, MMT acknowledges the need for additional routine trending of complaints at a more granular level.

In response to Observation 3A of the 483 response, MMT committed to perform a statistical analysis of complaints (see Attachment 16) to establish lot complaint alert thresholds. This analysis was approved on May 23, 2017 and SOP-QLC-QLE-00702, *Product Complaint Handling*, was revised on May 31, 2017 to include these thresholds (see Attachment 9). SOP-QLC-QLE-00702, *Product Complaint Handling* also details the actions required when a lot complaint alert threshold is exceeded, including notification to management, investigation (documented in (b) (4)) of root cause and identification and implementation of corrective action. (See response to Device QSR Requirements, section 1, subsection “Statistical Methodology and CAPA”, for further details on SOP-QLC-QLE-00702.) MMT acknowledges that while such alert thresholds identify lots that are statistical outliers, they do not serve as a substitute for routine trending of complaints across lots over time.

As detailed in the response to Observation 5 of the 483 response, MMT committed to implement the use of trend reports for analysis of complaints by finished product lot, manufacturing date, and component lot, which provides complaint trending between lots. While the plan for implementation of these new trend reports was issued on July 11, 2017 as committed in the response, details on the new trend reports were not explicitly referenced in the response. As such an updated version of SOP-QLC-QLE-00702, *Product Complaint Handling* (Attachment 12) was revised on September 26, 2017, and now includes the following new trending requirements:

- Trending will be performed by finished product lot, manufacturing date, and component lot.
- Trend analysis will cover all complaints subclasses, with additional focus on complaint subclasses with higher risks to patients.
- Trends will be analyzed by individual subclass and subclasses that are grouped by similar failure modes.
- Statistical rules will be used to analyze trend data. (See response to Device QSR Requirements, section 1, subsection “Statistical Methodology and CAPA” for additional detail.)

- When statistically significant changes in data are detected (e.g., outliers, shifts or trends), the SQOL will be notified and an investigation will be initiated (documented in (b) (4)) to determine the cause, impact, and CAPAs as appropriate.
- Trend reports will be reviewed (b) (4) by the SQRT and Product Technology.
- These new trend reports will be included in the Annual Product Records Review.

The revision of SOP-QLC-QLE-00702, *Product Complaint Handling* described above provides ongoing statistical analysis of additional complaint data that allows signal detection and CAPA based on inter-lot and intra-lot complaint trends.

MMT will also take the following **actions**:

- A new cross-functional Complaints Analysis Trend Team will be formed by November 1, 2017. The team will include colleagues responsible for Complaints management, Production, Quality, and Product Technology. A statistician will provide support to the team and the team will be chaired by the Combination Product Program Director. This team will analyze complaint trend data, support trend investigations including identification of CAPA and further refine complaint trend data presentation and statistical analysis.
- SOP-QLC-QLE-00702, *Product Complaint Handling* will be revised by November 30, 2017 to establish a link between the complaint trending process and review of the risk management file. The timing for notification and review of complaints trends and the risk management file will be based on the level of patient risk or statistical change in occurrence ranking.
- Complaint subclasses will be reviewed and SOP-QLC-QLE-00702, *Product Complaint Handling* will be revised by November 30, 2017 to provide guidance to Complaint Investigators on verifying/assigning complaint subclasses to ensure consistent classification in support of accurate trending.

(b) (4) Complaint Trend Analysis Data

Complaint data for EpiPen lots shipped (b) (4) through August 31, 2017 was analyzed for statistically significant outliers, shifts or trends. This data was analyzed by a cross functional team of colleagues from Complaints management, Production, Biomedical Technology, and Quality with the support of a statistician. The analysis can be found as Attachment 18.

The analysis by the cross functional team included a review of all complaints subclasses, with a focus on subclasses with a high severity ranking for harm to patient based on the outcome of MTR 17-021, *Complaint Prioritization Protocol* (Attachment 11). Trending of complaint subclasses was analyzed by manufacturing date, by EpiPen lot number and by component (Power Pak) lot number. Trending by manufacturing date and component lot number in addition to trending by EpiPen lot number allows detection of trend events that may be related to sequence of manufacture or specific components (Power Pak) lots which may not be apparent through trending by EpiPen lot number alone. In addition to trending by individual complaint subclasses, this analysis also included a group of four different complaint subclasses that all relate to device functionality. Trending of such a group allows detection of trend events that may be due to the same cause but that might not be apparent when trended by the individual subclasses.

The analysis of the grouped subclass Device Functionality as well as some of the individual subclasses included in this group (Proper Sequence Followed But Injection and or Activation Failed; Spontaneous Activation; Multiple Attempts Required to (Successfully) Inject Product; and (b) (4)) identified statistical outliers in December 2015 and March through May 2015 related to the 2017 recall of 22 EpiPen lots including Lot 5FA665. Of these data points, and as also discussed further in response to Drug cGMP Regulations section 1, Lot 5FA665 had the highest number of complaints, including the only complaints (2) with returned samples with confirmed (b) (4) defects. The charts also show other statistical outliers of lots not included in the 2017 recall, although none at the level of Lot 5FA665. The analysis concluded that an investigation into these data points should be conducted and QAR PR33456 has been initiated accordingly. Based on this statistical analysis, MMT believes further investigation of these outliers is warranted to better understand any potential product impact.

Notably, the trend analysis of other complaints subclasses (b) (4) with a high severity rating for potential harm to patient did not identify any data points or trends that require investigation, however these and all complaint subclasses will continue to be analyzed (b) (4)

DEVICE QSR REQUIREMENTS

Introduction

EpiPen was first approved by FDA in 1987, and has been regulated by FDA as a drug and subject to relevant cGMP regulations. In the time since FDA published its final rule clarifying cGMP requirements for combination products in 2013 and associated guidance in January 2017, MMT has been transitioning to a Quality System that fully integrates relevant streamlined QSR requirements for device constituent parts.

Since undergoing its first inspection in February to March 2017 where combination product cGMP was a focus, MMT is accelerating the process of integrating applicable requirements within 21 C.F.R. Part 820 to ensure they are met in a holistic manner. Below, MMT responds to FDA's concerns, and outlines its commitments to demonstrate its dedication to holistically integrating these QSR requirements as appropriate and in accord with FDA's streamlined combination product regulation and guidance. MMT also commits to conduct a comprehensive assessment of its systems against the QSR with oversight and input from a third-party cGMP consultant. This assessment will be incorporated into the CAP that was developed following the inspection.

Historically, as part of lifecycle management, MMT developed, manufactured, and assessed EpiPen in accord with drug cGMP requirements. MMT has, and continues to have, data and controls that support confidence in its processes to produce safe and effective product suitable for its intended use. MMT has implemented significant manufacturing controls as part of its manufacturing process for EpiPen. Controls have been defined in the Product Process Specifications for, among other things, component cleaning and preparation; aseptic filling; inspection; assembly; testing; packaging; and release testing. Extensive controls also exist for

suppliers and vendors to systemically evaluate incoming material and components to ensure the integrity of the final product once manufactured.

While MMT's manufacturing controls remain strong, the site will conduct a comprehensive review of all controls that impact final combination products, including supplier and vendor controls. The objective is to ensure EpiPen meets user needs and performs as intended, while reducing the potential for patient harm, as the site transitions to QSR compliance for the streamlined requirements. The review will reevaluate: (i) critical-to-function component dimensions, in which additional attributes are subjected to (b) (4) inspection and testing; (ii) in-process controls related to critical-to-safety and essential-to-function attributes; and (iii) test-and-release specifications. Appropriate actions will be taken as a result. The site also will take a holistic approach to review and assess its quality agreements and plans, complaints evaluation system, risk management documents, and design attributes associated with usability to further expand its current processes to fully incorporate device-specific QSR requirements applicable to combination products.

MMT will undertake a step-wise approach to apply design controls and requirements under 21 C.F.R. § 820.30 to currently marketed products, products subject to premarket review, and products intended to be marketed in the future. MMT also will implement other device-specific QSR requirements such as Purchasing Controls to improve its management of all suppliers and control of incoming components, as it enhances its Quality System.

MMT is committed to this transition for its combination products, and it will leverage its current drug cGMP systems and processes and incorporate QSR requirements with support from both internal and external expertise and resources.

- 1. Failure to adequately analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems, as required by 21 CFR 820.100(a)(1).**

Causes of Non-Conformities

In this section of the Warning letter, FDA notes that MMT committed in its 483 response to develop a procedure to assess the performance variability of the EpiPen assembly machine, including routine trending of action limits for the levels of components/units ejected by the different (b) (4). The Warning Letter also notes that MMT did not provide the procedure or explain how this variability data would be assessed or drive CAPA. The response below provides the procedure, summarizes the implementation status and commits to further action in this area.

As part of the response to Observation 4B of the 483 response, MMT has trended eject levels from the (b) (4) for (b) (4) lots of EpiPen Jr. Each eject has been categorized by severity to patient as a means to define priority of control measures, and this data has been statistically analyzed and used to establish interim action limits for (b) (4). This analysis is included in (b) (4), *Eject & Reject Analysis Report*

(Attachment18). The results for all assembled lots will be assessed versus these interim action limits as part of all EpiPen batch records by September 30, 2017. A draft example of the machine defect attribute chart is included as Attachment 20. These interim limits will be verified and revised as appropriate after data from a total of (b) (4) lots of EpiPen or EpiPen Jr have been collected. Based on the current manufacturing schedule, this data should be available by March 1, 2018. In the interim, the site will continuously evaluate outputs from this process.

A new procedure, SOP-MAN-GEN-11222, *In-Process Trending for Setting Action Limits in Filling, Inspection, and Assembly Operations*, was created (effective July 11, 2017) to manage the process of trending and setting action limits for machine ejects. The procedure was updated on September 25, 2017 to link the EpiPen assembly eject failure modes to patient risk in Table 1 of the procedure (Attachment 21). The procedure was also revised to require an investigation documented in (b) (4) for any batch that exceeds an eject action limit to understand the root cause of the higher eject rate, determine potential impact on product use, safety and other batches, and to determine appropriate CAPA. The procedure also specifies that (b) (4) should be considered as part of the root cause investigation.

SOP-MAN-GEN-11222, *In-process Trending for Setting Action Limits in Filling, Inspection, and Assembly Operations* and SOP-QLA-MQA-00006, *Site Quality Review Team and Quality Performance Management* (Attachment 22) have been revised to include the requirement for (b) (4) review of eject trend data by the site's cross-functional quality review team. This trend analysis will include a (b) (4) review period and an analysis of all statistically significant shifts or trends that have occurred in the reported (b) (4). This review will also determine the need to investigate any shifts or trends identified within the report, assess product impact and identify appropriate CAPA.

Actions:

As a further action, MMT commits to reviewing supplier Quality Agreements for critical components identified in the dFMEA and working with these suppliers to develop appropriate control strategies for the identified high-risk components. These strategies may include the trending of critical quality attributes and a periodic review of supplier process capabilities by the SQRT. These control enhancements are scheduled to be completed by March 1, 2018.

The interim limits for ejects from the EpiPen assembly machine will be verified and revised as appropriate after data from a total of (b) (4) lots of EpiPen or EpiPen Jr have been collected. Based on the current manufacturing schedule, this data should be available by March 1, 2018. In the interim, the site will continuously evaluate outputs from this process.

Process Capabilities

In this section of the Warning Letter, FDA states that MMT does not use appropriate statistical methodology to assess process capability of the production at critical process steps to identify recurring quality issues. FDA also notes that in its 483 response, MMT did not provide procedures it committed to develop to assess the capability of production equipment, and did not explain how MMT plans to analyze and use this data to drive CAPA and whether upstream/downstream processes will be considered in capability analyses.

MMT's prior controls for assessing in-process capabilities have relied, in part, on analyzing final-product attributes. MMT has developed quality measures to enhance its in-process capabilities for detecting and addressing potential nonconformities on a statistical basis. Namely, MMT committed to implementing routine equipment capability studies as well as periodic reviews of ongoing trend analyses relating to in-process issues. In response to the Warning Letter, the site also has undertaken actions to enhance these commitments by developing methods to monitor the equipment capability studies, specifying how the site will analyze and use this data to drive CAPAs, and monitoring potential impact to upstream and downstream processes.

Specifically, as part of the response to Observation 4C1-3 of the 483 response, MMT developed a procedure to evaluate process capability (i.e., Cpk or Ppk) on each unit operation of product manufacturing. SOP-QLA-GEN-11104, *Conducting Process and Machine Capability Studies* (Attachment 23), provides instructions on determining process capability. The procedure has since been revised to require process mapping, the identification of product attributes along with their impact on patient safety, critical process parameters, and (b) (4) process capability review by the SQRT. If the capability does not meet the limits defined in SOP-QLA-GEN-11104, *Conducting Process and Machine Capability Studies* an investigation will be initiated in (b) (4) to determine root cause, assess product and patient impact, evaluate upstream and downstream processes as needed, and identify CAPA as appropriate.

These studies will be the basis of an ongoing program to monitor and improve the overall process capability and will be included in the Annual Product Record Review. SOP-QLA-MQA-00710, *Annual Products Records Reviews* (Attachment 24) has been revised to reflect this requirement. We are confident that these additional enhancements will further strengthen our overall control model.

Statistical Methodology and CAPA

In this section of the Warning Letter, FDA notes that, while the commitment in the 483 response stated MMT would now use statistical analysis to identify potential complaint trends within a lot ("intra-lot"), it did not address limits for recurring complaints not associated with a lot or how complaint trending links to CAPAs. The response below summarizes the current complaint trend analysis requirements and how this trending links to identification and implementation of CAPAs.

Following FDA's observations, MMT first revised its process for complaint trending to better identify recurring quality problems and/or causes of nonconforming product. As part of the revised process, MMT implemented a statistical-based methodology for evaluating complaint trends, in addition to other statistical tools that had been used for assessing trend alerts and directing CAPAs. At the time, such methodology was limited to intra-lot complaints. Since then, MMT has further revised and enhanced its complaint-trending process by, for example, expanding its statistical approach beyond intra-lot complaints, using statistical analysis to better define a trend, and bolstering the link between complaint trending and CAPA implementation. The response below better summarizes the current status of MMT's complaint-trending system and actions developed to address FDA's concerns.

For purposes of the discussion below, complaint “class” and “subclass” are categories that describe the nature of a quality complaint. As an example, “Injectables” is a class of complaint and “Spontaneous Activation” is one of several associated subclasses.

Complaint Trending by Class by GPQC/DAT

As discussed during the inspection and as detailed in response to Observation 3C of the 483 response, the Pfizer corporate Global Product Quality Complaint/Data Analysis and Trending Team (“GPQC/DAT”) uses statistical methodology to analyze complaints for potential trends (b) (4) by product and class. The (b) (4) different statistical rules used by GPQC/DAT to detect potential trends are detailed in procedure QCG073, *GPQC/DAT Trend Alert and Outlier Reports* (Attachment 14). These rules compare the complaint counts by class in the current period to (b) (4) and more recent periods. For example, one of these rules is whether complaints (b) (4) are more than (b) (4) from the (b) (4) and another rule is whether complaints (b) (4).

The rules used by GPQC/DAT provide robust statistical analysis of complaint trends at the class level, independent of an obtained lot number.

When the GPQC/DAT statistical rules detect a potential trend, a Complaint Trend Alert is generated and GPQC/DAT evaluates the data versus the criteria in GPQC/DAT procedure QCG060, *Complaints Data Analysis and Trending Process* (Attachment 15), to determine whether a Complaint Trend Notification (“TN”) should be issued. If so, a TN is sent to Pfizer corporate and site Quality Operations management and the Pfizer Quality Authority responsible for the product. MMT site procedure, SOP-QLC-QLE-00702, *Product Complaint Handling* (Attachment 12), specifies that TNs received from GPQC/DAT require an investigation (documented in (b) (4)) to determine the cause, scope, impact, CAPAs as appropriate, and whether regulatory notification is required. The statistical trending by GPQC/DAT by complaint class and the GPQC/DAT and MMT procedures addressing TNs, establish the link between complaint trending at the class level and CAPA.

Improvements Made to Complaint Trending by Subclass

As detailed in response to Observation 5 of the 483 response, MMT committed to implement the use of trend reports for analysis of complaints by finished product lot, manufacturing date, and component lot, which is intended to provide trending of complaints between lots (inter-lot) by subclass over time. This new trend analysis by MMT focuses on complaint subclasses with higher risks to patients. While the plan for implementation of this new trending was issued on July 11, 2017 as committed in the 483 response, details on the new trend reports were not included in the response. SOP-QLC-QLE-00702, *Product Complaint Handling* (Attachment 12) was revised on September 26, 2017 to include the new trending requirements. The revised procedure requires the application of statistical rules for the analysis of complaint data for trends by subclass for finished product lots, manufacturing dates, and component lots. Statistical analysis included in the procedure includes control charting using statistical process control rules (e.g., control limits based on (b) (4), a trend based on (b) (4), and a shift based on (b) (4)).

SOP-QLC-QLE-00702, *Product Complaint Handling* also provides a link to CAPA as part of this new trending process. When statistically significant changes in data are detected (e.g., outliers, shifts or trends), the procedure requires that the SQOL is notified and an investigation is initiated (documented in (b) (4)) to determine the cause, impact, and CAPAs as appropriate. Also per the procedure, these trend reports will be reviewed (b) (4) by the SQRT and the Product Technology group. In addition, the new trend reports will be included in the Annual Product Records Review.

As mentioned in Drug cGMP Regulations, section 2, in the subsection titled “Trend Analysis”, a new cross-functional Complaints Analysis Trend Team will be formed by November 1, 2017. The team will include personnel responsible for Complaint Management, Production, Quality, and Product Technology. A statistician will provide support to the team and the team will be chaired by the Combination Product Program Director. This team will analyze complaint trend data, support trend investigations including the identification of CAPA as appropriate. This team will also be assigned the responsibility of further refining complaint trend data presentation and statistical analysis.

An analysis by MMT of this new trend data can be found as Attachment 18. The results of this trend analysis are discussed in Drug cGMP Regulations, section 2, in the subsection titled “Trend Analysis”. This analysis will serve as a starting point, and will include incoming materials to post-market surveillance, for the work of the new Complaints Analysis Trend Team.

2. Failure to adequately establish and maintain procedures for verifying the device design, as required by 21 CFR 820.30(f). Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

MMT recognizes the need for continual design verification of its products as part of lifecycle management and is committed to ensure that its products meet the requirements of design control and the QSR. MMT will not use AQL sampling as a basis for acceptance criteria during design verification. As part of product life cycle management, MMT recognizes the need to assess the capability of its verification of design inputs requirements and expected design outputs and has begun this exercise. Each output will be evaluated subject to patient risk and its essential impact on device functionality. This evaluation will be performed based on the impact of device failure risk levels presented in Table 1 below, recognizing that EpiPen is classified as a Critical Device.

Table 1: Essential Use Characteristics

Essential Use Attribute	Specification	User Need
(b) (4)	(b) (4) – (b) (4) ml	(b) (4)
	(b) (4) – (b) (4) lbf	
	(b) (4) – (b) (4) mm for EpiPen	
	(b) (4) – (b) (4) mm for EpiPen Jr	
	NMT (b) (4)	
	(b) (4) – (b) (4) lbf.	
	Needle (b) (4) to (b) (4)	
Auto-injector does not activate with safety in place	(b) (4) lbf.	Prevent injury to user and/or patient and activation of device before intended. Ensure the auto-injector is suitable for use when needed
Resist inadvertent activation during handling	Auto-injector does not self-activate during arming	Prevent injury to user and/or patient and activation of device before intended use. Ensure the auto-injector is suitable for use when needed

Table 2: Product classification risk levels and corresponding reliability specification

Risk Level	Impact of Device Failure	Reliability Specification	Confidence Level
Critical	Device failure that creates a hazard that could result in a death or serious injury	(b) (4) %	(b) (4) %
Major	Device failure that creates a hazard that could result in a non-serious adverse event including minor, temporary, or medically reversible adverse events	(b) (4) %	
Minor	Device failure may result in pain or discomfort or other inconveniences	(b) (4) %	

MMT initiated a reevaluation of the risk assessment for each product input and corresponding output requirement based on EpiPen's *Hazards Analysis List*, PR 31372. This initial risk assessment was completed by a cross functional team which assigned a Risk Criticality ranking to each use input and output requirement based on severity of risk to the customer: Critical to Safety; Essential to Function; and Supporting Requirement, in PR 31384, *EpiPen NGA Autoinjector System Level Risk Assessment* (Attachment 25). The current EpiPen design requirements designated as Critical to Safety or Essential to Function must demonstrate a SLR of (b) (4) % at (b) (4) % confidence level with (b) (4) during Design Verification testing as documented in PR 31379, *EpiPen NGA Autoinjector System Level Reliability Rationale* (Attachment 26). In reevaluating the design criteria under our ongoing continuous improvement

program, MMT is committed to move the SLR (b) (4) % at (b) (4) % reliability confidence level with (b) (4) during Design Verification testing.

As a result, MMT is reevaluating the design specifications with respect to the design outputs as part of our continuous improvement program. This assessment will evaluate critical component dimensions, mold capability studies and tolerance analysis as they relate to the function and safe use of the EpiPen product. This evaluation will also examine the controls in place for component manufacturing that assure that component assemblies perform to meet the patient need. The number of samples to be tested during Design Verification for a product classified as Critical per Table 1 will be determined using (b) (4) Software Ver. (b) (4) (an industry recognized, validated, commercially available software product).

- The sample plan will be based on attribute sampling.
- Based on the product classification risk levels and corresponding reliability specification as noted above in Table 2, a UQL of (b) (4) will be used to calculate the sample size required to demonstrate a SLR (b) (4) % at (b) (4) % confidence level.
- This sample plan, as a (b) (4) ((b) (4)), based on a UQL of (b) (4), dictates a sample size of (b) (4) units.

With successful testing based on a UQL of (b) (4), a calculated reliability coverage of (b) (4) % (as noted by the operating characteristics of the sampling plan) will be demonstrated with (b) (4) % confidence which (b) (4) % reliability requirement noted in Table 2.

Action:

To ensure alignment of design outputs to design inputs and design verification acceptability, MMT will execute a Design Traceability Matrix based on the requirements contained in SOP-DVL-PRT-00003, *Design Outputs for New Products, Major Changes to Existing Products and Changes Affecting Product/ User Interaction* (Attachment 27).

MMT commits to completing design verification for its approved combination products, including EpiPen:

- Revise design verification procedure SOP-DVL-PRT-00004, *Design Verification and Validation for New Products, Major Changes to Existing Products and Changes Affecting Product/User Interaction*, by November 30, 2017 to reflect enhanced process and documentation in Design History File.
- Approve final report of design verification by December 31, 2018, including (b) (4), for the EpiPen NGA Auto-Injector.
- A detailed timeline for EpiPen design verification will be developed based on product lifecycle design assessments. This plan will be included in the next 483 quarterly update (by October 31, 2017).

3. Failure to adequately establish and maintain procedures for validating the device design. Design validation shall ensure that devices conform to defined user needs and

intended uses. Design validation shall include risk analysis, where appropriate, as required by 21 CFR 820.30(g).

User Needs and Intended Uses

MMT has evaluated EpiPen's design and manufacturing process and developed controls to ensure that the product is manufactured to meet established user needs, intended uses, and other design and development requirements. MMT acknowledges that there are opportunities to further align its design validation procedures with QSR requirements for medical devices or device constituent parts of combination products.

Throughout the product lifecycle, MMT has continually and carefully reviewed its processes relating to product development and manufacturing to ensure EpiPen, as a finished product, meets predefined user needs and intended uses. MMT has established these user needs and intended uses in a design input document PRD/TRD 13-003, rev. 2, *Product and Technical Requirements Document, EpiPen Truject Next Generation Autoinjector with (b) (4) (NGA)*. The company also has conducted risk analyses for design and use-related issues (see Device QSR Requirements section 3, subsection "Risk Analysis" for related documents) to evaluate potential hazards associated with the use of the device and to implement appropriate mitigations for patient risk.

Moreover, MMT has established incoming component, in-process and release controls that ensure EpiPen is manufactured to perform consistent with its intended use. For example, as part of final release, EpiPen products require functional testing of samples from (b) (4) lots (b) (4) for critical functions. Critical functions include (b) (4), with such testing demonstrating that product is performing as expected and meeting its intended use on a consistent basis.

Identification and testing for human factors and product usability are critical components of design validation, especially for these injector products. The company understands the importance of these factors as design inputs, and that its products must meet user needs consistently. Even though MMT has traditionally manufactured EpiPen according to drug cGMP requirements, the company incorporated specific QSR elements such as human-factors analysis as part of the product lifecycle. For example, MMT used human factors data to inform the design of the current EpiPen products during development.

More recently, MMT assessed currently marketed EpiPen products against ANSI/AAMI/IEC 62366-1:2015, *Medical devices – Part 1: Application of usability engineering to medical devices*, Annex C — a recognized consensus standard for human factors. The purpose of this review was to create a usability engineering file and assure that the risk management file identifies risks caused by usability problems of the user interface. Based on this assessment, MMT created a usability engineering file which is now included in the Design History File ("DHF") for EpiPen. The following documents are contained in the Design History File and attached to this response:

- PRD/TRD PRD/TRD 13-003, rev. 2, *Product and Technical Requirements Document, EpiPen Truject Next Generation Autoinjector (b) (4) (NGA)* (Attachment 28)
- R01-878, *uFMEA for EpiPen NGA Auto-injector* (Attachment 29)

- MTR 17-003, *EpiPen Complaint Data Evaluation* (Attachment 30)
- MTR 17-019, *Risk Mitigation through Device and Labeling Design for EpiPen NGA Auto-Injector* (Attachment 31)
- MTR 17-007, *EpiPen NGA Residual Risk Analysis* (Attachment 32)

As noted above in the introduction to the QSR section of the Response, MMT is transitioning to a validation process incorporating specific device QSR requirements for its combination products. This transition applies to approved products, (b) (4), and future product to be developed by the company. MMT is committing to the following activities for its combination products:

Action:

- SOP-DVL-PRT-00004, *Design Verification and Validation for New Products, Major Changes to Existing Products and Changes Affecting Product/User Interaction* will be updated to include all required design validation elements for combination products and to set forth the process for conducting design validation (by November 30, 2017).
- For EpiPen products:
 - Comprehensive review of user needs (by February 2018);
 - Update risk analyses as appropriate (by February 2018);
 - Performing human factors formative studies as applicable (by February 2018);
 - Submitting a human factors summative validation protocol, for review by the Agency, which will be applicable to all EpiPen products (March 2018);
 - Execution of the summative validation protocol (by October 2018); and
 - Submitting an overall design validation summary report including an HFE/UE report summarizing all human factors and usability engineering work including the human factors validation study (by January 2019).
- Develop a schedule for completing the activities above for other approved products (by November 2017).

In addition to the changes in procedure MMT agrees to update the design verification activities as described in response to QSR Regulations section 2.

Risk Analysis

MMT understands the significance a risk analysis plays in design controls for medical device and device constituent parts for combination products. The risk management activities document known product hazards, evaluate risks associated with use of the device, device design, and manufacturing process, and identify mitigations to eliminate or reduce their occurrence.

MMT acknowledges that, as noted during the inspection, MMT was not actively updating its risk assessments under the QSR, though it was assessing the product's risk profile under drug GMPs and as part of its annual review process. Since the 2017 inspection, MMT has also performed and updated its risk analysis consistent with QSR.

During the development of the currently marketed EpiPen products, a thorough design Failure Modes Effects Analysis ("dFMEA") was conducted. Through the dFMEA, the function of each

component was evaluated along with the potential risks associated with the component failing to perform its function. These risks were documented accordingly. A use Failure Modes Effects Analysis (“uFMEA”) has also been conducted to evaluate and document use-related risks. More recently, a HAL was created to evaluate the severity of harm due to the combination product failing to perform its intended function. A gap analysis was conducted between the HAL and the FMEA documents to ensure alignment in the assessment of potential harm.

Action:

Going forward, the HAL will be updated based on signals received from the field by monitoring the complaint and adverse event data from the field. The dFMEA and uFMEA risk assessments will be reviewed based on any updates to the HAL, or at a minimum, annually per SOP-QLA-MQA-00710, *Annual Products Record Review*. MMT is providing the following documents to demonstrate its compliance with QSR risk-analysis requirements for combination products:

- PR 33187, *EpiPen NGA TruJect Auto-Injection Design FMEA* (Attachment 33)
- R01-878, *uFMEA for EpiPen NGA Auto-injector* (Attachment 29)
- PR 33375, *Hazard Analysis List* (Attachment 10) (PR 33375 is an updated version of the HAL; the prior version of the HAL, PR 31372, is discussed in Device QSR Requirements, section 2.)
- SOP-QLA-MQA-00710, *Annual Products Record Review* (Attachment **Error! Reference source not found.**)

MMT also commits to perform a pFMEA and integrate it into the site’s overall risk management process. MMT will perform the pFMEA by March 2018.

Quality Agreements

In this section of the Warning Letter, FDA notes that, notwithstanding the Quality Agreement (“QA”) between MMT and Mylan, MMT is ultimately responsible for the quality of combination products manufactured at the site. MMT agrees, and is committed to carrying out its responsibility for the quality of all products manufactured at the site.

MMT, as contract manufacturer for its customer Mylan, is responsible for manufacturing product in compliance with applicable cGMP requirements. To ensure clear assignment of responsibilities in line with cGMP, MMT and Mylan have a Quality Agreement (“QA”) in place. The current QA between MMT and Mylan explains MMT’s responsibility to comply with cGMP at each manufacturing step, and conforms to standards outlined in FDA’s guidance document titled Contract Manufacturing Arrangements for Drugs: Quality Agreements (“QA Guidance”). For example, MMT is responsible under the QA for the following responsibilities:

(b) (4)

(b) (4)

MMT is also responsible for compliance with specific QSR requirements (21 CFR parts 4.4(b), 210, 211, 820.10, 820.30, 820.50, and 820.100) for activities carried out at the site. Among other things, MMT is responsible for:

(b) (4)

MMT remains committed to manufacturing product in compliance with cGMP.

As an improvement, MMT commits to conduct an assessment of its QA with Mylan by October 31, 2017. The goal of the assessment will be to identify opportunities to expand the current QA to improve express alignment with both QSR requirements and drug cGMP regulations. Among other things, the assessment will ensure that responsibility for the following are captured in a detailed form in the updated QA:

- Compliance with applicable regulatory provisions (e.g. 21 CFR Part 4 and Part 820);
- Management responsibilities;
- Purchasing controls;
- Design controls;
- Device validation;
- Design history file management;
- Management of component device suppliers;
- Device release testing;
- CAPAs;
- Review AE and quality complaint data at periodic site quality review meeting; and
- Device master record and technical documentation.

Following identification of opportunities for improvement, MMT will work with Mylan to establish a revised QA that incorporates those improvements.

MMT also notes that it has a comprehensive pharmacovigilance agreement (“PVA”) in place, which was updated in 2016, with Mylan that outlines the reporting of adverse events and other

safety information related to EpiPen products. Specifically, the parties exchange information related to adverse events, exposure to product during pregnancy or lactation, suspected overdose, medication errors, misuse, abuse, off-label use, (b) (4)

Both parties also have pharmacovigilance audit rights.

Among other things, the PVA requires both parties to:

- Maintain a safety database;
- Assess individual case reports for adverse events in their territory and share the assessed report with the other party on expedited and pre-defined timelines depending upon the severity of the reported adverse event;
- Exchange adverse events and trends across all markets;
- Prepare aggregate reports for submission in its respective territory; and
- Conduct on-going review and analysis of all information pertinent to the safety profile of the Product, and notify the other party of a confirmed safety risk.

With the updated QA and the PVA in place between MMT and Mylan, MMT believes its Quality System is well supported and positioned to continue to supply product in conformance with cGMP, with the benefit of effective post-market surveillance. MMT's operations will be further bolstered following the assessment and revision of the current QA.

Repeat Violations at Facility

In this section of the Warning Letter, FDA notes that it cited similar cGMP violations in both the October to November 2014 and February to March 2017 inspections, but did not identify any particular observations as repeats in the Warning Letter. Nonetheless, MMT appreciates that similar subsystems were involved (e.g., complaint management and investigations) in the 2014 and 2017 inspections. MMT recognizes the significance of FDA inspectional observations and the importance of developing holistic and sustainable CAPAs to address the observations and prevent their recurrence.

MMT believes that it has continued to improve its Quality System since the 2014 inspection, with a particular focus on investigations and complaint management. For example, MMT formed a joint team with its commercial partner to assess opportunities for process enhancements or customer communications to reduce the number of complaints across high-frequency categories. In addition, MMT committed to update its complaint handling procedure to:

- Include a historical review in the investigation;
- Document in the investigation other complaints received for the same issue;
- Quantify in the investigation the number of complaints received to date; and
- Require electronic documentation when a complaint is received.

As a result of the 2017 inspection, MMT committed to take additional significant actions to improve its Quality System. For example, MMT has committed to CAPAs to address specific concerns regarding its investigation and complaint-management process:

- Conduct a retrospective review of complaints, a retrospective product review, and several product tests related to the Power Pak (b) (4) issue;

- Revise its notification to management procedure to ensure that formal escalation occurs for any OOS result, whether for finished product, in-process sample, or incoming component, and to require an assessment of the potential impact of the OOS to marketed product;
- Include full lot traceability in investigations for incoming component failures; and
- Revise its procedures to require disassembly of complaint units associated with FTA, DTA, cloudy/discolored solution, spontaneous activation, and particulate matter complaints, regardless of the condition of the sample returned.

Although the Warning Letter did not specifically identify which observations from the prior inspection are viewed as repeats, MMT will address FDA's concerns comprehensively and effectively. MMT believes in a directed, robust response to any FDA observation, with appropriate CAPAs and effectiveness checks to ensure compliance. To that end, as noted above, MMT will retain a third-party cGMP consultant to conduct effectiveness checks of the CAPAs implemented as a result of its CAP.

Attachments

1. SOP-QLA-GEN-00802, Ver. 11.0, *Site Change Management Process*, with associated templates, TMP-DSG-DEV-CHG-01, Ver. 1.0, *Design Change Decision*, TMP-DSG-DEV-CHG-02, Ver. 1.0, *Design Change Impact Assessment*, TMP-DSG-DEV-CHG-03, Ver. 1.0, *Design Change Action Plan*, and TMP-DSG-DEV-CHG-04, Ver. 1.0, *Design Change Project Closure Review*
2. JA-DVL-PDV-10803, Ver. 1.0, *Complaint Sample Evaluation Job Aid*
3. JA-DVL-PDV-10803, Ver. 2.0, *Complaint Sample Evaluation Job Aid*
4. JA-DVL-PDV-10803, Ver. 3.0, *Complaint Sample Evaluation Job Aid*
5. JA-DVL-PDV-10803, Ver. 4.0, *Complaint Sample Evaluation Job Aid*
6. JA-DVL-PDV-10803, Ver. 5.0, *Complaint Sample Evaluation Job Aid*
7. (b) (4), September 26, 2017, *Summary Report for Protocol (b) (4) Quality and Patient Assessment of EpiPen Related Quality Assurance Reports (QARs) from (b) (4)*
8. GPB-QS1073, Version 13.0, *Prioritization of Pfizer Product Quality Complaints*
9. SOP-QLC-QLE-00702, Version 17.0, *Product Complaint Handling*
10. PR 33375, Rev. 2.0, *Hazard Analysis List, EpiPen Auto-Injector (Epinephrine)*
11. MTR 17-021, September 25, 2017, *EpiPen Complaint Sub-Class Prioritization By Corresponding Risk to Patient Safety*
12. SOP-QLC-QLE-00702, Version 19.0, *Product Complaint Handling* (to become effective on October 10, 2017)
13. (b) (4), September 26, 2017, *Quality Retrospective Assessment of Product Complaints for EpiPen*
14. QCG073, Ver. 2.0, *GPQC DAT Trend Alert and Outlier Reports*
15. QCG060, Ver. 11.0, *Quality Complaint Data Analysis and Trending Process*
16. SR-2017-GLL-027, May 23, 2017, *EpiPen Injectable Complaint Thresholds*
17. SOP-QLC-QLE-00702, Version 16.0, *Product Complaint Handling*
18. MTR-17-023, September 26, 2017, *EpiPen/EpiPen Jr/Epinephrine Auto-Injector Complaint Trend Analysis, Lots Shipped (b) (4) through (b) (4), Complaints Received (b) (4) through (b) (4)*
19. (b) (4), September 19, 2017, *Eject & Reject Analysis Report (b) (4), Machine (b) (4) Reject Data Collection on NGA Line (b) (4)*
20. FP-F-M/F-N, Ver. 3.0, page 60 of 97, *Packaging and Inspection Master Specification, Epinephrine Injection, USP Auto-Injector*
21. SOP-MAN-GEN-11222, Ver. 2.0, *In-process Trending for Setting Action Limits in Filling, Inspection, and Assembly Operations*

22. SOP-QLA-MQA-00006, Ver. 7.0, *Site Quality Review Team and Quality Performance Management*
23. SOP-QLA-GEN-11104, Ver. 2.0, *Conducting Process and Machine Capability Studies*
24. SOP-QLA-MQA-00710, Ver. 18.0, *Annual Product Records Reviews*
25. PR 31384, July 27, 2017, *EpiPen NGA Autoinjector Systems Level Risk Assessment*
26. PR 31379, July 6, 2017, *EpiPen NGA Autoinjector System Level Reliability Rationale*
27. SOP-DVL-PRT-00003, Ver. 4.0, *Design Outputs for New Products, Major Changes to Existing Products and Changes Affecting Product/ User Interaction*
28. PRD/TRD 13-003, Rev. 2, *Product and Technical Requirements Document, EpiPen Truject Next Generation Autoinjector with (b) (4) (NGA)*
29. R01-878, PR 33331, September 25, 2017, *Use-FMEA, EpiPen NGA Auto-Injector*
30. MTR 17-003, February 15, 2017, *EpiPen Complaint Data Evaluation (b) (4)*
31. MTR 17-019, September 20, 2017, *Risk Mitigation through Device and Labeling Design for EpiPen NGA Auto-Injector*
32. MTR 17-007, February 17, 2017, *EpiPen NGA Residual Risk Analysis*
33. PR 33187, Rev. 2.0, *EpiPen NGA Truject Auto-Injector Design FMEA*